Growth and Intellectual Abilities of Six-Year-Old Children with Congenital Heart Disease

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Abstract: OBJECTIVE To determine growth and its relationship to IQ in children with congenital heart disease (CHD) undergoing cardiopulmonary bypass surgery within the first year of life. STUDY DESIGN Prospective single-center cohort study on 143 children (91 males) with different types of CHD (29 univentricular). Children with recognized genetic disorders were excluded. Growth (weight, height, and head circumference [HC]) was assessed at birth, before surgery, and at 1, 4, and 6 years and compared with Swiss growth charts. IQ was assessed at 6 years using standardized tests. Univariate and multivariable linear regressions were performed to determine predictors of HC and IQ at 6 years. RESULTS HC at birth was in the low average range (33rd percentile, P = .03), and weight (49th percentile, P = .23) and length (47th percentile, P = .06) were normal. All growth measures declined until the first surgery, with a catch-up growth until 6 years for height (44th percentile, P = .07) but not for weight (39th percentile, P = .003) or for HC (23rd percentile, P < .001). Children undergoing univentricular palliation showed poorer height growth than other types of CHD (P = .01). Median IQ at 6 years was 95 (range 50-135). Lower IQ at 6 years was independently predicted by lower HC at birth, lower socioeconomic status, older age at first bypass surgery, and longer length of intensive care unit stay. CONCLUSIONS Smaller HC at birth and postnatal factors are predictive of impaired intellectual abilities at school age. Early identification should alert clinicians to provide early childhood interventions to optimize developmental potential.

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Growth and intellectual abilities at six years in congenital heart disease

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Keywords: Neurodevelopmental Outcome, Growth Trajectories, Head Growth

Abstract

Objective: To determine growth and its relationship to IQ in children with congenital heart disease (CHD) undergoing cardiopulmonary bypass surgery within the first year of life.

Study Design: Prospective single-center cohort study on 143 children (91 males) with different types of CHD (29 univentricular). Children with recognized genetic disorders were excluded. Growth (weight, height and head circumference (HC)) was assessed at birth, before surgery, at one, four and six years and compared to Swiss growth charts. IQ was assessed at six years using standardized tests. Univariate and multivariable linear regressions were performed to determine predictors of HC and IQ at six years.

Results: HC at birth was in the low average range (33^{th} percentile, p=0.03), while weight (49^{th} percentile, p=0.23) and length (47^{th} percentile, p=0.06) were normal. All growth parameters declined until the first surgery, with a catch-up growth until six years for height (44^{th} percentile, p=0.07) but not for weight (39^{th} percentile, p=0.003) or for HC (23^{th} percentile, p<0.001). Children undergoing univentricular palliation showed poorer height growth than other types of CHD (p=0.01). Median IQ at six years was 95 (range 50 to 135). Lower IQ at six years was independently predicted by lower HC at birth, lower socioeconomic status, older age at first bypass surgery, and longer length of intensive care unit stay.

Conclusion: Smaller head circumference at birth and postnatal factors are predictive of impaired intellectual abilities at school age. Early identification should alert clinicians to provide early childhood interventions to optimize developmental potential.

Introduction

Children with congenital heart disease (CHD) are at risk of poor somatic growth, [1] particularly those with univentricular heart disease. [2] Many studies report growth for the first years of life, but fewer report long-term anthropometric outcome, most often for weight and height. (2–5)[2–5] and less so for head circumference (HC). [1,6,7] Determinants of growth retardation are multifactorial and include genetic traits, [8] hemodynamic factors related to the underlying CHD with altered cerebral and somatic blood perfusion. [5] Prenatal onset of poor growth may occur and has been linked to abnormal hemodynamic state. [9]

Small preoperative HC and poor postnatal head growth is related to impaired neurodevelopmental outcome from early childhood until adolescence in biventricular (10–14)[10–14] and univentricular(6,15–18)[6,15–18] types of CHD undergoing cardiopulmonary bypass surgery (CPB). Results for weight and height are conflicting. While some studies have not found any association, [15,19] others have demonstrated that birth weight [8] and low height trajectories were related to poorer neurodevelopmental outcome at 14 months. [20] However, the link between early growth and school-age outcome has not been determined for children with CHD.

Our aims were to describe growth trajectories from birth until six years of life and the relationship with IQ in children with CHD undergoing infant CPB surgery. We also sought to evaluate risk factors for lower head circumference and poorer IQ at six years of life.

Patients and Methods

Design

The current study is an analysis of a prospective study evaluating neurodevelopmental outcome after open-heart surgery. [21,22]

Study population

Between May 2004 and July 2009, 368 children with CHD undergoing CPB at the University Children's Hospital Zurich were preoperatively enrolled. They were subsequently examined at one, four, and six years of age. The exclusion criteria for this analysis were CPB prior to inclusion (n=42), age older than one year at first CPB surgery (n=58), a recognizable genetic or phenotypic syndrome (n=80), gestational age below 32 0/7 weeks and birth weight below 2000g (n=7). Of the 181 remaining eligible patients, 14 died before the first examination and two between the one-year and four-year examinations. Six children moved away, and in 16 cases, the parents could not be reached or refused participation. Thus, information on growth and neurodevelopmental outcome at six years was available for 143 participants. Demographic, cardiac, and surgical characteristics did not differ between excluded and included children except for use of deep hypothermia during first CPB, which was used less often in the participants (p=0.03, Table 1; online).

All demographic data were prospectively collected as described previously. [22] Socioeconomic status (SES) was determined based on maternal education and paternal occupation; each was scored from one to six, resulting in a score ranging from two to twelve. [23]

Cardiac diagnoses and severity of CHD were categorized as follows: univentricular and biventricular CHD, presence of cyanosis, and complexity of cardiac defect as proposed by Clancy et al. (cardiac anatomy with presence of aortic arch obstruction, Class I-IV with increasing complexity). [24]

The study was approved by the Institutional Review Board (No.19/04), and parents or caregivers provided written consent.

Surgical and perioperative characteristics

Two cardiac surgeons performed CPB surgery in normothermia or mild hypothermia (rectal temperature higher than 32°C). For details on the surgical management, please see Naef et al. [22]

Intensive care unit (ICU) management depended on the subsequent clinical course and complications, such as prolonged intubation, infections, sepsis, pneumothorax, chylothorax, renal insufficiency, peritoneal and hemodialysis, and seizures. Thirty-three patients (23%) were fed with a gastrointestinal tube at admission for cardiac surgery. At the one-year exam, only one patient (1%) still needed a gastrointestinal tube.

Growth measurements

Birth data were obtained retrospectively from birth records and hospital charts. Prospective measurements of weight, height and HC were performed the day before surgery and at one, four, and six years by a trained study nurse. Data were transformed to standard deviation scores (SDSs) based on Swiss growth charts. [25] Growth restriction or microcephaly was defined by a SDS below 3rd percentile and small for gestational age (SGA) as SDS weight and/or SDS length at birth below 10th percentile.

Neurodevelopmental assessment

At the six-year follow-up assessment, cognition was assessed with the third German version of the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III). [26] Three children were tested with the German versions of the Snijders Oomen Non-verbal Test of Intelligence because they had a developmental and/or speech and language delay. [27] Another three children were tested in the Italian-speaking region of Switzerland and were examined with the third Italian version of the Wechsler Intelligence Scale for Children (WISC). To report overall cognitive function, we combined the IQs of all the tests applied.

Statistical analysis

Data was analyzed with R (R Foundation for Statistical Computing, Vienna Austria) and SPSS 24.0 0 (IBM Corp., Armonk, N.Y.). Frequencies (percent) are given for categorical variables. Continuous parameters are presented as median and range, and correlations were performed with Spearman's rank correlation. Growth and growth trajectories were evaluated by converting the median SDS of children with CHD for height, weight, and HC measured at different ages into the corresponding quantile for normal children according to the Swiss growth charts. [25] Wilcoxon signed-rank tests were applied to determine whether the median SDS for children with CHD was significantly below 0 and to compare the SDS of children with CHD at different ages. CHD subclasses were compared along the years in a linear mixed model. This model included a random child effect to take account of dependencies induced by multiple measurements on the same child. To explore the determinants of HC and IQ at 6 years, both univariate and multivariable linear regressions were performed, including SDS of height, weight, and HC at birth and prior to surgery, gestational age, SGA, SES, gender, cardiac class, age at surgery, use of deep hypothermic circulatory arrest, total extracorporeal circulation time (log2-transformed), length of ICU stay (log2-transformed), and length of hospital stay (log2-transformed). For the multivariable analysis, a stepwise backward regression was carried out including all predictors for which the p-value was <0.2 in the univariate analysis. We found some high collinearity among early growth parameters and among clinical variables (Table 2; online). Thus, in addition to the full models, a series of multivariable models was analyzed, each including a single growth parameter. Hypothesis tests were 2-sided, and p-values <0.05 were considered statistically significant. For all regression analyses, SDS below -4 or above 4 were set to -4 and 4 respectively to reduce the effect of outliers.

Results

Study population

Median gestational age at birth was 39.7 weeks (range 32.2 to 42.0), of whom 11 (8%) patients were born between 32nd and 37th week of gestation. Median age at CPB surgery was 1.2 months (range 0.1 to 10.7). Median age at the follow-up assessments was one year (range 0.9 to 1.7), 4.3 years (range 3.9 to 4.7), and 6.3 years (range 5.8 to 6.7). Selected patient characteristics are shown in Table 3. The 143 patients (91 male) reflect a wide range of CHD, with dextro-transposition of great arteries (d-TGA) being the most frequent CHD (29%, n=42). Seventy-one percent (101) had a cyanotic heart defect, of whom 29 (20% of whole sample) had a univentricular physiology.

Growth pattern

Growth trajectories are presented in Figure 1 (A-C), and the proportion of children with growth restriction (< 3rd percentile) for each time point is shown in Figure 2.

At birth, median weight (49th percentile, SDS -0.03, range -2.92 to 3.76) and height (47th percentile, SDS -0.08, range -3.84 to 4.22) were within the norm (weight p=0.23, height p=0.06), while the rate of growth restriction (SDS < 3rd percentile) was 11% for weight and 13% for height (both p <0.001). The rate of children born SGA was 24%. We found median HC at birth in the low average range (33th percentile, SDS -0.43, range -4.89 to 2.86), which was significantly lower than the norm (p=0.03). The rate of microcephaly (SDS < 3rd percentile) was 11% (p<0.001).

Until the first CPB, all growth parameters declined, most markedly for weight (Figure 1). All growth parameters improved thereafter, and particularly within the first year of life. At six years, height (44th percentile, median SDS -0.16, range -2.46 to 1.90) was within the norm (p=0.07), while weight (39th percentile, median SDS -0.29, range -4.07 to 3.11, p=003) and especially HC (23th percentile, median SDS -0.75, range -4.43 to 2.11, p<0.001) remained below the norm. Growth trajectories of children with CHD are presented in relation to normative growth curves in supplemental Figure 3A-F (online).

Growth trajectories of children with univentricular CHD and those with a d-TGA are presented in supplemental Figure 4 (online). Children with univentricular CHD showed poorer height growth until six years of age (p=0.01), while weight (p=0.23) and HC (p=0.59) were similar to biventricular defects. Children with a d-TGA (n=42, 29%) had better height (p=0.01) and weight (p=0.04) growth than children with other types of CHD, but HC trajectory did not differ (p=0.83).

Risk factors for HC and IQ at six years

SES and growth measures at birth and surgery were related to HC at six years, as shown in the univariate analysis (Table 4). In the multivariable regression analysis, HC at birth and at first CPB surgery, SGA, and SES contributed 46% of the variance in HC at six years. Cardiac diagnoses (presence of cyanosis, cardiac class), gender, and gestational age were not associated with HC at six years. If the multivariable models were run with only one growth variable included each together with SES and ICU stay, growth parameters were retained in each of the models (Table 5; online).

Median IQ at six years was 95 (range 50 to 135), with 7 patients (5%) performing below 70 (p compared to norm=0.03, for details see [22]). Both patient and perioperative factors contributed to IQ at six years. This was significant for the following variables in the univariate analysis: GA, SES, use of DHCA, length of stay at ICU, birth weight, born SGA, and HC at birth (Table 4). In the multivariable analysis, lower SES, smaller HC at birth, older age at first CPB surgery, and longer ICU stay were independent risk factors for a lower IQ at six years (Table 4), with an explained variance of 30%. If SES was excluded from the model, the explained variance decreased to 16%. If only one growth variable was included in the multivariable model together with the other covariables, the only difference was found for SGA at birth and height at birth: both were significantly associated with IQ at six years (Table 6; online). Since TGA patients were operated during the neonatal period (<30 days) but only one of the patients with ventricular septal defect and none of the TOF patients, we included cardiac diagnosis as a categorical factor in addition to age at operation in our model. The effect of age

was not significant (beta=-0.01, p=0.67) anymore, while the effect of diagnosis remained significant (p=0.036) with lower IQ scores for children with TOF.

We also examined a variety of other potential risk factors (e.g. gastrointestinal tube feeding, need for preoperative intubation, preoperative catecholamines, total number of cardiac CPB surgeries, lowest temperature during surgery, use of low-flow circulation, antegrade cerebral perfusion), none of which were significantly related to HC or IQ at six years of age (data not shown). These findings were independent of the underlying cardiac anatomy (single ventricle versus biventricular CHD).

HC at six years correlated with IQ in biventricular CHD (r=0.32, p<0.001), but not in univentricular CHD (r=0.06, p=0.78) with an interaction term (HC at six years and type of CHD) that was almost significant (p=0.06).

Discussion

The aims of this study were to describe growth patterns until the age of six years for children with CHD undergoing CPB surgery and to examine the relationship between growth and intellectual abilities at six years. At birth, weight and height was normal, but HC was significantly below the norm. All growth parameters declined until CPB surgery, following which catch-up growth occurred, resulting in normal values for height and near normal for weight at six years of age, while HC remained significantly below the norm. Importantly, IQ at six years was independently predicted by HC at birth, socioeconomic status, age at first bypass surgery, and length of intensive care unit stay, but not by weight or length.

Our results expand those of previous studies, which demonstrated abnormal growth for all parameters during the first few months of life in children with a similar spectrum of CHD diagnoses. [1,7] The etiology of poor weight and height growth is thought to be multifactorial. Several factors may contribute to this phenomenon, including insufficient caloric intake, feeding difficulties, and non-

nutritive factors such as the altered expression of growth factors in association with pulmonary hypertension. [28] As almost one third of our population had a diagnose of d-TGA and were operated within the first days of life, physiological postnatal weight loss may to some extend account for the marked decline in weight before CPB. In contrast, impaired HC growth reflects brain growth, which can be affected prenatally. [29]

Importantly, children with a univentricular CHD showed particularly poor height growth or stunting (Figure 4B; online), a phenomenon that has been shown to persist after Fontan repair. [2,3,5] in contrast, children with d-TGA had normal growth except for HC. This long-lasting effect on HC in children with d-TGA is a new finding. Previous reports only showed poorer HC growth until 2 years of age. [30] The etiology remains elusive. However, limited fetal brain perfusion and redirected nutritional factors from the right ventricle to the descending aorta and to the lower part of the body, and preoperative hemodynamic stability seems to play a substantial role in later brain development. [31]

As HC remained below normal until the age of six years, we determined risk factors for poor HC: lower HC at birth and at first surgery, SGA status, and lower SES were the only risk factors for poorer HC at six years of age, explaining 46 percent of the variance. These findings are in agreement with previous studies [6,10,11] and demonstrate that cardiac and surgical variables appear to have less impact on brain growth, assuming head growth reflects brain growth, than was shown previously. [32]

We identified HC at birth, SES, length of ICU stay and age at first surgery as independent predictors of IQ at six years. These risk factors have been consistently reported, and the latter two are potentially modifiable. [8,13,14,18] Older age at surgery was a risk factor for poorer IQ in our cohort, but only if we did not control for cardiac diagnosis . Although it is assumed that surgical intervention in neonates may be more harmful for the developing brain, [33] evidence is available that waiting for surgical repair is associated with poorer motor outcome and a higher frequency of brain injury due to persistent hypoperfusion. [10,34] Importantly, age at surgery was strongly confounded by the cardiac diagnosis:

TGA patients were operated during the neonatal period, but only one of the patients with ventricular septal defect and none of the TOF patients. When we included the cardiac diagnosis as a categorical factor in the statistical model (TOF, TGA, ventricle septal defect, other), the effect of age was not significant anymore, suggesting that our effect of age could be due to a confounding effect of diagnosis.

Our finding that HC at birth is an important predictor of IQ confirms previous studies that have demonstrated a relationship between poor fetal head growth [35] or small HC at birth and neurodevelopmental outcome in early childhood, [6,10,13,15,16,18] pre-school age, [11,17] and adolescence. [14] There is consistent evidence that intrauterine brain growth is altered in children with complex CHD, starting at around 30 weeks gestation, [29] resulting in smaller HC and smaller brain volumes at birth. [36,37] Etiological factors include reduction of umbilical vein oxygen saturation, altered blood streaming, and reduced oxygen content in the ascending aorta. [38]

We found postoperative ICU stay to strongly predict IQ. This potentially modifiable risk factor has been identified by many studies, [10,17,39] and may be a surrogate marker for surgical and postoperative complexity with negative impact on later neurodevelopmental outcome. [20]

A variety of other risk factors for poor IQ have been identified in other studies. For example, feeding problems have been associated with poorer growth trajectories and poorer neurodevelopmental outcome in infancy and early childhood. [13,15,16] We also examined this variable, but could not find a significant association after controlling for other risk factors. This may be because we examined long-term outcome, during which early neurological disturbances may be mitigated as children develop and other factors, such as SES, become more important. Further, stunting (low height z-score trajectories) has been related to poor neurodevelopmental performance at early age. [15,20] We found a correlation of low birth weight and SGA with IQ only in the univariate analysis, but not in the multivariable model. This is supported by Miller et al.'s findings that growth asymmetry was not associated with early outcome. [6]

Interestingly, six-year HC only correlated with IQ for children with a biventricular CHD, but not for those with an univentricular CHD. A possible explanation might be that HC in univentricular CHD does not reflect brain volume. This has been shown in children undergoing Fontan repair, where HC at age 2-3 years was found within the normal range but brain volumes were smaller than in control children. One explanation for this discrepancy is that intracranial volume is determined not only by brain volume but also by cerebrospinal fluid volume, which was larger in this particular group, probably as a result of hemodynamic changes specific to the surgical repair in these children. [33]

Limitation

Our study is limited by the heterogeneity of types of CHD, resulting in relatively small sample sizes for CHD subgroups. Some results may not be significant due to lack of power. Especially, the link between HC and IQ in univentricular CHD needs to be investigated in bigger cohort. Another limitation arises from inclusion of late preterm patients, who are at risk for impaired neurocognitive outcome. [40] This limitation has been addressed by including GA as an independent variable in the statistical model. A methodological limitation arises from the collinearity of some of our predictors (Table 2; online). This possibly causes an issue for the interpretation of our selected model, since when two strong predictors are too much correlated, only one of them will be selected. Thus, the absence of a predictor in our selected model does not necessarily imply that this is a weak predictor, it could also be redundant with another predictor already in the model. Further, we did not perform fetal or neonatal cerebral MRI, which would allow to relate HC to brain growth, volume, and cerebral lesions. Caloric intake was not measured continuously, and thus we could not assess the role of nutrition on growth. The growth curves we present come from a single-center, ethnically homogeneous sample, thus growth trajectories in other centers may differ, depending on patient population characteristics and perioperative management. Anthropometric data at birth were collected retrospectively and may be of limited accuracy.

Conclusion

Children with CHD undergoing CPB may show persistent poor head growth until school age paralleled by poorer intellectual abilities. Weight and height growth show a decline prior to surgery, followed by near complete catch-up growth for weight and complete catch-up growth for height. Other risk factors for poorer intellectual outcome include lower SES, older age at surgery, and longer ICU stay. Future research is needed for a better understanding of fetal factors causing altered brain development to allow for timely interventions, and on improving postoperative management to shorten postoperative stay and thus improve long-term outcome for children with CHD.

Acknowledgements

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Abbreviations

BSID II	Bayley Scales of Infant Development II
CHD	Congenital heart disease
CPB	Cardiopulmonary bypass
d-TGA	Dextro-Transposition of great arteries
HC	Head circumference
ICU	Intensive care unit
IQ	Intelligence quotient
SDS	Standard deviation score

References

1. Daymont C, Neal A, Prosnitz A, Cohen MS. Growth in Children With Congenital Heart Disease. Pediatrics. 2013 Jan 1;131(1):e236–42.
2. Burch PT, Ravishankar C, Newburger JW, Lambert LM, Pemberton VL, Granger S, et al. Assessment of Growth 6 Years after the Norwood Procedure. J Pediatr. 2017 Jan;180:270–4.e6.
3. François K, Bové T, Panzer J, Groote KD, Vandekerckhove K, Wilde HD, et al. Univentricular heart and Fontan staging: analysis of factors impacting on body growth. Eur J Cardiothorac Surg. 2012 Jun 1;41(6):e139–45.
4. Dalili M, Meraji SM, Davari P, Moghaddam MYA, Abkenar HB, Vahidi A, et al. Growth status of Iranian children with hemodynamically important congenital heart disease. Acta Med Iran. 2011;49(2):103–8.
5. Vogt KN, Manlhiot C, Van Arsdell G, Russell JL, Mital S, McCrindle BW. Somatic Growth in Children With Single Ventricle Physiology: Impact of Physiologic State. J Am Coll Cardiol. 2007 Nov 6;50(19):1876–83.
6. Miller TA, Zak V, Shrader P, Ravishankar C, Pemberton VL, Newburger JW, et al. Growth Asymmetry, Head Circumference, and Neurodevelopmental Outcomes in Infants with Single Ventricles. J Pediatr. 2016 Jan;168:220–5.e1.
7. Poryo M, Paes LA, Pickardt T, Bauer UMM, Meyer S, Wagenpfeil S, et al. Somatic Development in Children with Congenital Heart Defects. J Pediatr. 2018 Jan 1;192:136–43.e4.
8. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, et al. Neurodevelopmental Outcomes After Cardiac Surgery in Infancy. Pediatrics. 2015 May 1;135(5):816–25.
9. Williams IA, Fifer WP, Andrews H. Fetal Growth and Neurodevelopmental Outcome in Congenital Heart Disease. Pediatr Cardiol. 2015 Mar 10;36(6):1135–44.
10. Limperopoulos C, Majnemer A, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital

heart defects. J Pediatr. 2002 Jul;141(1):51–8.

11. Majnemer A, Limperopoulos C, Shevell M, Rosenblatt B, Rohlicek C, Tchervenkov C. Long-term Neuromotor Outcome at School Entry of Infants with Congenital Heart Defects Requiring Open-heart Surgery. J Pediatr. 2006 Jan;148(1):72–7.
12. von Rhein M, Buchmann A, Hagmann C, Huber R, Klaver P, Knirsch W, et al. Brain volumes predict neurodevelopment in adolescents after surgery for congenital heart disease. Brain. 2014 Jan;137(1):268–76.
13. Mussatto KA, Hoffmann R, Hoffman G, Tweddell JS, Bear L, Cao Y, et al. Risk Factors for Abnormal Developmental Trajectories in Young Children With Congenital Heart Disease. Circulation. 2015 Aug 25;132(8):755–61.
14. Matos SM, Sarmento S, Moreira S, Pereira MM, Quintas J, Peixoto B, et al. Impact of Fetal Development on Neurocognitive Performance of Adolescents with Cyanotic and Acyanotic Congenital Heart Disease. Congenit Heart Dis. 2014 Sep 1;9(5):373–81.
15. Medoff-Cooper B, Irving SY, Hanlon AL, Golfenshtein N, Radcliffe J, Stallings VA, et al. The Association among Feeding Mode, Growth, and Developmental Outcomes in Infants with Complex Congenital Heart Disease at 6 and 12 Months of Age. J Pediatr. 2016 Feb 1;169:154–9.e1.
16. Goldberg CS, Lu M, Sleeper LA, Mahle WT, Gaynor JW, Williams IA, et al. Factors Associated with Neurodevelopment for Children with Single Ventricle Lesions. J Pediatr. 2014 Sep;165(3):490-496.e8.
17. Rotermann I, Logoteta J, Falta J, Wegner P, Jung O, Dütschke P, et al. Neuro-developmental outcome in single-ventricle patients: is the Norwood procedure a risk factor? Eur J Cardiothorac Surg 2017 Sep 1;52(3):558-564.
18. Hangge PT, Cnota JF, Woo JG, Hinton AC, Divanovic AA, Manning PB, et al. Microcephaly is associated with early adverse neurologic outcomes in hypoplastic left heart syndrome. Pediatr Res. 2013 Jul;74(1):61–7.

19. Knirsch W, Zingg W, Bernet V, Balmer C, Dimitropoulos A, Prêtre R, et al. Determinants of body weight gain and association with neurodevelopmental outcome in infants operated for congenital heart disease. Interact Cardiovasc Thorac Surg. 2010 Mar 1;10(3):377–82.
20. Ravishankar C, Zak V, Williams IA, Bellinger DC, Gaynor JW, Ghanayem NS, et al. Association of Impaired Linear Growth and Worse Neurodevelopmental Outcome in Infants with Single Ventricle Physiology: A Report from the Pediatric Heart Network Infant Single Ventricle Trial. J Pediatr. 2013 Feb;162(2):250–6.e2.
21. Krueger JJ, Brotschi B, Balmer C, Bernet V, Latal B. Postoperative Hyperglycemia and 4-Year Neurodevelopmental Outcome in Children Operated for Congenital Heart Disease. J Pediatr. 2016 Jan;168:258.
22. Naef N, Liamlahi R, Beck I, Bernet V, Dave H, Knirsch W, et al. Neurodevelopmental Profiles of Children with Congenital Heart Disease at School Age. J Pediatr. 2017 Sep;188:75-81.
23. Largo RH, Pfister D, Molinari L, Kundu S, Lipp A, Duc G. Significance of prenatal, perinatal and postnatal factors in the development of AGA preterm infants at five to seven years. Dev Med Child Neurol. 1989 Aug;31(4):440–56.
24. Clancy RR, McGaurn SA, Wernovsky G, Spray TL, Norwood WI, Jacobs ML, et al. Preoperative risk-of-death prediction model in heart surgery with deep hypothermic circulatory arrest in the neonate. J Thorac Cardiovasc Surg. 2000 Feb;119(2):347–57.
25. Braegger C, Jenni OG, Konrad D, Molinari L. Neue Wachstumskurven fuer die Schweiz. Paediatrica. 2011;22(1).
26. Petermann F. Wechsler Preschool and Primary Scale of Intelligence – III German Edition. Frankfurt/Main: Pearson Assessment; 2009.
27. Snijders JT, Snijders-Oomnen N. Snijders-Oomen Non-Verbal Intelligence Test-Revised. Lisse, Netherlands: Swets Test Publishers; 1985.
28. Chung H-T, Chang Y-S, Liao S-L, Lai S-H. The effects of corrective surgery on endothelial

biomarkers and anthropometric data in children with congenital heart disease. J Int Med Res. 2017 Apr 1;45(2):493–503.

29. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, et al. Brain Volume and Metabolism in Fetuses With Congenital Heart Disease Evaluation With Quantitative Magnetic Resonance Imaging and Spectroscopy. Circulation. 2010 Jan 5;121(1):26–33.
30. Rosti L, Frigiola A, Bini RM, Giamberti A, Pomè G, Chessa M, et al. Growth After Neonatal Arterial Switch Operation for D-Transposition of the Great Arteries. Pediatr Cardiol. 2014 May 1;23(1):32–5.
31. Peyvandi S, De Santiago V, Chakkarapani E, Chau V, Campbell A, Poskitt KJ, et al. Association of Prenatal Diagnosis of Critical Congenital Heart Disease With Postnatal Brain Development and the Risk of Brain Injury. JAMA Pediatr. 2016 Apr;170(4):e154450.
32. Burnham N, Ittenbach RF, Stallings VA, Gerdes M, Zackai E, Bernbaum J, et al. Genetic factors are important determinants of impaired growth after infant cardiac surgery. J Thorac Cardiovasc Surg. 2010 Jul;140(1):144–9.
33. Heye KN, Knirsch W, Latal B, Scheer I, Hahn A, Wetterling K, et al. Reduction of brain volumes after neonatal cardiopulmonary bypass surgery in single ventricle congenital heart disease prior to Fontan completion. Pediatr Res. 2018 Jan;83(1-1):63-70.
34. Lynch JM, Buckley EM, Schwab PJ, McCarthy AL, Winters ME, Busch DR, et al. Time to surgery and preoperative cerebral hemodynamics predict postoperative white matter injury in neonates with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg. 2014 Nov;148(5):2181–8.
35. Hahn E, Szwast A, Cnota J, Levine JC, Fifer CG, Jaeggi E, et al. Association between fetal growth, cerebral blood flow and neurodevelopmental outcome in univentricular fetuses. Ultrasound Obstet Gynecol. 2016 Apr 1;47(4):460–5.
36. von Rhein M, Buchmann A, Hagmann C, Dave H, Bernet V, Scheer I, et al. Severe Congenital

Heart Defects Are Associated with Global Reduction of Neonatal Brain Volumes. J Pediatr. 2015 Dec;167(6).1259-1263.e1.

37. Owen M, Shevell M, Donofrio M, Majnemer A, McCarter R, Vezina G, et al. Brain Volume and Neurobehavior in Newborns with Complex Congenital Heart Defects. J Pediatr. 2014 May;164(5):1121–7.e1.
38. Sun L, Macgowan CK, Sled JG, Yoo S-J, Manlhiot C, Porayette P, et al. Reduced Fetal Cerebral Oxygen Consumption Is Associated With Smaller Brain Size in Fetuses With Congenital Heart Disease. Circulation. 2015 Apr 14;131(15):1313–23.
39. International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Impact of Operative and Postoperative Factors on Neurodevelopmental Outcomes After Cardiac Operations. Ann Thorac Surg. 2016 Sep 1;102(3):843–9.
40. Johnson S, Evans TA, Draper ES, Field DJ, Manktelow BN, Marlow N, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. Arch Dis Child Fetal Neonatal Ed. 2015 Jul;100(4):301–8.

Figure legends

Figure 1. Median growth indices over time

Median growth indices over time for 143 children with congenital heart defect for standard deviation score of weight, height, and head circumference. Horizontal lines depict median and upper and lower boundary 75th and 25th percentile; empty dots represent outliers. SDS, standard deviation score.
* $p<0.05$, ‡ $p<0.001$

Figure 2. Proportion of children with growth below the 3rd percentile for each age

Proportion of children with growth indices below the 3rd percentile for each age. White depicts weight, light grey depicts height, black depicts head circumference. SDS, standard deviation score.

Figure 3A-F; online. Growth trajectories of children with congenital heart disease in relation to Swiss normative growth curves

Figure 4A-F; online. Growth trajectories for univentricular CHD and d-TGA

Mean of growth trajectories for children with univentricular congenital heart disease (CHD) and dextro-transposition of great arteries (d-TGA) compared to the sample.

Table 1; online only

Table 1. Characteristics of included and excluded patients

Characteristic at Baseline	Included (n=143)	Excluded (n=38)	*p-value*
Male	91 (63)	22 (58)	*0.52*
Gestational age (wk)	39.7 (32.2 – 42.0)	39.7 (34.4 – 41.2)	*0.36*
Small for gestational age	35 (24)	9 (24)	*0.92*
Apgar at 5 minutes	9 (1 – 10)	9 (5 – 10)	*0.55*
Socioeconomic status	8 (2 – 12)	8 (3 – 12)	*0.93*
Cardiac Diagnosis			
Univentricular CHD	29 (20)	11 (29)	*0.25*
Cyanotic CHD	101 (71)	28 (74)	*0.71*
Age at 1st CPB surgery (months)	1.2 (0.1 - 10.7)	0.47 (0.1 – 9.0)	*0.12*
Use of DHCA	25 (18)	13 (34)	*0.03*
Cumulative ECC (min)	196 (40 - 818)	228 (70 – 715)	*0.053*
Intensive care unit stay (days)	7 (1 - 232)	10 (3 – 156)	*0.06*
Weight at birth (SDS score)	-0.03 (-2.9 – 3.8)	-0.36 (3.2 – 3.6)	*0.78*
Weight at surgery (SDS score)	-1.20 (-5.8 – 1.9)	-0.76 (-6.9 – 2.6)	*0.49*
Height at birth (SDS score)	-0.08 (-3.8 – 4.2)	-0.54 (-2.8 – 2.2)	*0.78*
Height at surgery (SDS score)	-0.62 (-6.4 – 2.6)	-0.76 (-7.3 – 2.1)	*0.82*
Head circumference at birth (SDS score)	-0.43 (-4.9 – 2.9)	-0.89 (-4.2 – 3.8)	*0.30*
Head circumference at surgery (SDS score)	-0.80 (-4.8 – 2.9)	-1.06 (-11.4 – 1.9)	*0.81*

CPB, cardiopulmonary bypass surgery; DHCA, deep hypothermic cardiac arrest; ECC, extra corporal circulation; SDS, standard deviation score.

Table 2; online only

Table 2. Collinearity among risk factors for head circumference and IQ at six years of age

	GA	SES	Male gender	Cardiac Class	Age at surgery	Use of DHCA	Cum. ECC	ICU stay	Hospital stay	Weight at birth	Weight at surgery	Height at birth	Height at surgery	SGA	HC at birth	HC at surgery
GA		0.128	0.048	-0.100	0.015	0.014	-0.04	-0.037	0.010	0.478‡	0.162	0.336‡	0.174*	-0.465‡	0.329†	0.263†
SES	0.128		-0.114	-0.037	0.017	0.045	0.095	0.028	0.010	0.150	0.023	0.016	-0.049	-0.012	0.053	0.074
Male gender	0.048	-0.114		-0.027	-0.159	0.003	-0.029	0.071	0.001	0.021	0.184*	0.094	0.093	-0.009	-0.107	0.060
Cardiac Class	-0.100	-0.037	-0.027		-0.035	0.316‡	0.567‡	0.278†	0.249†	0.051	0.021	0.044	-0.025	-0.041	0.081	0.007
Age at surgery	0.015	0.017	-0.159	-0.035		-0.385‡	-0.187*	-0.397‡	-0.381‡	-0.132	-0.444‡	-0.121	-0.212*	0.108	-0.123	-0.273†
Use of DHCA	0.014	0.045	0.003	0.316‡	-0.385‡		0.341‡	0.303‡	0.299‡	-0.007	0.157	-0.021	0.078	-0.005	-0.035	0.107
Cum. ECC	-0.040	0.095	-0.029	0.567‡	-0.187*	0.341‡		0.521‡	0.535‡	0.109	0.135	0.108	0.057	-0.075	0.065	0.061
ICU stay	-0.037	0.028	0.071	0.278†	-0.397‡	0.303‡	.521‡		0.755‡	-0.040	0.085	-0.016	-0.042	0.035	-0.174*	-0.051
Hospital stay	0.025	0.010	0.001	0.249†	-0.381‡	0.299‡	0.535‡	0.755‡		-0.075	-0.066	-0.095	-0.202*	0.048	-0.142	-0.123
Weight at birth	0.478‡	0.150	0.021	0.051	-0.132	-0.007	0.109	-0.040	-0.075		0.598‡	0.757‡	0.568‡	-0.711‡	0.665‡	0.577‡
Weight at surgery	0.162	0.023	0.184*	0.021	-0.444‡	0.157	0.135	0.085	-0.066	0.598‡		0.582‡	0.840‡	-0.491‡	0.401‡	0.718‡
Height at birth	0.336‡	0.016	0.094	0.044	-0.121	-0.021	0.108	-0.016	-0.095	0.757‡	0.582‡		0.719‡	-0.705‡	0.555‡	0.543‡
Height at surgery	0.174*	-0.049	0.093	-0.025	-0.212*	0.078	0.057	-0.042	-0.202*	.0568‡	0.840‡	0.719‡		-0.523‡	0.427‡	0.672‡
SGA	-0.465‡	-0.012	-0.009	-0.041	0.108	-0.005	-0.074	0.048	0.035	-0.711‡	-0.491‡	-0.705‡	-0.523‡		-0.471‡	-.0452‡
HC at birth	0.329‡	0.053	-0.107	0.081	-0.123	-0.035	0.065	-0.174*	-0.142	0.665‡	0.401‡	0.555‡	0.427‡	-0.471‡		0.695‡
HC at surgery	0.263†	0.074	0.060	0.007	-0.273†	0.107	0.061	-0.051	-0.123	0.577‡	0.718‡	0.543‡	0.672‡	-0.452‡	0.695‡	

Values are Spearman correlations between patient characteristics and medical variables. GA, gestational age; SES, socioeconomic status, DHCA, deep hypothermic circulatory arrest; cum. ECC, cumulative extra corporal circulation time; HC, head circumference; ICU, intensive care unit.
* $p<0.05$, † $p<0.01$, ‡ $p<0.001$

Table 3. Demographic characteristics of patient population

Characteristic at Baseline	n=143
Male No. (%)	91 (63)
Birth weight (gr)	3300 (2060 – 5250)
Birth length (cm)	49 (42 – 57)
Birth head circumference (cm)	34 (30 – 38)
Gestational age (wk)	39.7 (32.2 – 42.0)
Small for gestational age No. (%)	35 (24)
Apgar at 5 minutes	9 (1 – 10)
Socioeconomic status	8 (2 – 12)
Cardiac Diagnosis	
Biventricular CHD No. (%)	114 (80)
d-TGA No. (%)	42 (29)
Other cyanotic No. (%)[a]	30 (21)
Other acyanotic No. (%)[b]	42 (29)
Univentricular CHD No. (%)	29 (20)
Cardiac Diagnose Classes	
2 ventricles, no arch obstruction (Class I) No. (%)	100 (70)
2 ventricles, arch obstruction (Class II) No. (%)	14 (10)
1 ventricle, no arch obstruction (Class III) No. (%)	14 (10)
1 ventricle, arch obstruction (Class IV) No. (%)	15 (10)

Values are expressed as n (%) or median (range).

[a] Cyanotic congenital heart disease (CHD) despite dextro-transposition of great arteries (d-TGA) included biventricular repair in patients with Tetralogy of Fallot (n=14), total anomalous pulmonary venous connection (n=5), common arterial trunk (type I in n=5, type II in n=1), pulmonary atresia (with intact ventricular septum in n=1, with ventricular septal defect in n=2), Ebstein's anomaly associated with valvar pulmonary stenosis (n=1), hemitruncus arteriosus (n=1).

[b] Other acyanotic CHD included isolated ventricular septal defect (n=19), ventricular septal malalignment (n=1), atrioventricular septal defect (complete in n=5, partial in n=1), ostium secundum atrial septal defect (n=1), sinus venosus atrial septal defect (n=1), coarctation of the aorta (n=3), interrupted aortic arch (type A in=1, type B in=2), aortic valve stenosis (n=3), valvular pulmonary stenosis (n=2), Bland-White-Garland syndrome (n=2), left-position of great arteries (n=1).

Table 4

Table 4. Analysis of risk factors for head circumference and IQ at six years of age

		Head circumference at six years			IQ at six years		
		Univariate		*Multivariable* R^2=0.46	*Univariate*		*Multivariable* R^2=0.30
	n (%) or median (range	β (CI)	R^2	β (CI)	β (CI)	R^2	β (CI)
Gestational age (weeks)	39.7 (32.2 – 42.0)	0.06 (-0.06 – 0.18)	0	-	**0.09 (0.002 – 0.17)***	**0.02**	-
Socioeconomic status	8 (2 – 12)	**0.10 (0.01 – 0.19)***	**0.03**	**0.09 (0.02 – 0.17)***	**0.14 (0.08 – 0.20)‡**	**0.11**	**0.15 (0.09 – 0.21)‡**
Male gender No. (%)	91 (63)	0.09 (-0.33 – 0.51)	0	-	0.15 (-0.17 – 0.46)	0	-
Cardiac Class	1 (1-4)	0.08 (-0.12 – 0.27)	0	-	-0.07 (-0.21 – 0.08)	0	-
Age at 1st CPB surgery (months)	1.2 (0.1 - 10.7)	-0.03 (-0.10 – 0.04)	0	-	**-0.04 (-0.09 – 0.02)**	**0.006**	**-0.08 (-0.14 – -0.02)†**
Use of DHCA No. (%)	25 (17.5)	0.22 (-0.31 – 0.76)	0	-	**0.41 (0.02 – 0.81)***	**0.02**	-
Cumulative ECC (min)[a]	196 (40 - 818)	0.009 (-0.21 – 0.22)	0	-	-0.05 (-0.21 – 0.11)	0	-
Intensive care unit stay (days)[a]	7 (1 - 227)	**-0.14 (-0.32 – 0.04)**	**0.01**	-	**-0.15 (-0.29 – -0.02)***	**0.03**	**-0.22 (-0.36 – -0.07)†**
Hospital length of stay (days) [a]	24 (7 – 232)	-0.13 (-0.34 – 0.08)	0.003	-	**-0.14 (-0.30 – 0.02)**	**0.01**	-
Weight at birth (SDS)	-0.03 (-2.9 – 3.8)	**0.38 (0.23 – 0.54)‡**	**0.14**	-	**0.13 (0.004 – 0.25)***	**0.02**	-
Weight at surgery (SDS)	-1.20 (-5.8 – 1.9)	**0.28 (0.16 – 0.40)‡**	**0.13**	-	0.04 (-0.05 – 0.14)	0	-
Height at birth (SDS)	-0.08 (-3.8 – 4.2)	**0.31 (0.17 – 0.45)‡**	**0.12**	-	0.11 (-0.002 – 0.22)	0.02	-
Height at surgery (SDS)	-0.62 (-6.4 – 2.6)	**0.22 (0.10 – 0.33)‡**	**0.09**	-	0.03 (-0.06 – 0.13)	0	-
Small for gestational age No. (%)	35 (24)	**-0.56 (-1.02 – -0.10)***	**0.03**	**0.53 (0.04 – 1.01)***	**-0.38 (-0.72 – -0.03)***	**0.03**	-
Head circumference at birth (SDS)	-0.43 (-4.9 – 2.9)	**0.46 (0.34 – 0.58)‡**	**0.31**	**0.31 (0.15 – 0.46)‡**	**0.20 (0.10 – 0.30)‡**	**0.10**	**0.17 (0.08 – 0.27)†**
Head circumference at surgery (SDS)	-0.80 (-4.8 – 2.9)	**0.45 (0.34 – 0.56)‡**	**0.34**	**0.35 (0.20 – 0.49)‡**	0.09 (-0.01 – 0.19)	0.02	-

Bold numbers represent factors included in the multivariable analysis.

CPB, cardiopulmonary bypass surgery; DHCA deep hypothermic circulatory arrest; ECC, extra corporal circulation; SDS Standard deviation score; β, regression coefficient; R^2, adjusted coefficient of determination

CI, confidence interval

[a] Due to non-normal distribution, the natural logarithm was used for the regression analysis.

* $p<0.05$, † $p<0.01$, ‡ $p<0.001$

Table 5; online only

Table 5. Multivariable analysis of risk factors for head circumference at six years of age

	Multivariable R^2=0.17 β (CI)	*Multivariable* R^2=0.21 β (CI)	*Multivariable* R^2=0.17 β (CI)	*Multivariable* R^2=0.12 β (CI)	*Multivariable* R^2=0.07 β (CI)	*Multivariable* R^2=0.35 β (CI)	*Multivariable* R^2=0.39 β (CI)
Socioeconomic status	*NS*	0.104 (0.02-0.19)*	0.104 (0.01-0.20)*	0.119 (0.03-0.21)*	0.047 (0.00-0.20)*	0.087 (0.01-0.17)*	0.101 (0.02-0.18)*
Intensive care unit stay (days)[a]	*NS*	-0.209 (-0.39 - -0.03)*	-0.196 (-0.38 - -0.01)*	*NS*	*NS*	*NS*	*NS*
Weight at birth (SDS)	0.416 (0.24-0.59) ‡	-	-	-	-	-	-
Weight at surgery (SDS)	-	0.324 (0.19-0.46) ‡	-	-	-	-	-
Height at birth (SDS)	-	-	0.307 (0.16-0.46)‡	-	-	-	-
Height at surgery (SDS)	-	-	-	0.236 (0.12-0.36)†	-	-	-
Small for gestational age	-	-	-	-	-0.690 (-1.21 - -0.17)*	-	-
Head circumference at birth (SDS)	-	-	-	-	-	0.463 (0.34-0.59)‡	-
Head circumference at surgery (SDS)	-	-	-	-	-	-	0.468 (0.35-0.58)‡

β, regression coefficient; CI, confidence interval, R^2, adjusted coefficient of determination; SDS, Standard deviation score

[a] Due to non-normal distribution, the natural logarithm was used for the regression analysis.

* p<0.05, † p<0.01, ‡ p<0.001

- not included in the model, NS included in the model but not significant

Table 6; online only

Table 6. Multivariable analysis of risk factors for IQ at six years of age

	Multivariable R^2=0.22 β (CI)	*Multivariable* R^2=0.22 β (CI)	*Multivariable* R^2=0.27 β (CI)	*Multivariable* R^2=0.22 β (CI)	*Multivariable* R^2=0.26 β (CI)	*Multivariable* R^2=0.30 β (CI)	*Multivariable* R^2=0.22 β (CI)
Gestational age (weeks)	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*
Socioeconomic status	0.154 (0.09 – 0.22)‡	0.154 (0.09 – 0.22)‡	0.152 (0.09 – 0.22)‡	0.154 (0.09 – 0.22)‡	0.156 (0.09 – 0.22)‡	0.150 (0.09 – 0.21)‡	0.154 (0.09 – 0.22)‡
Age at 1st CPB surgery (months)	-0.087 (-0.15 - -0.03)†	-0.087 (-0.15 - -0.03)†	-0.067 (-0.13 - -0.01)*	-0.087 (-0.15 - -0.03)*	-0.077 (-0.14 - -0.02)*	-0.079 (-0.14 - -0.02)†	-0.09 (-0.15 - -0.03)†
Use of DHCA No. (%)	*NS*	*NS*	0.426 (0.02 – 0.84)*	*NS*	*NS*	*NS*	*NS*
Intensive care unit stay (days)[a]	-0.255 (-0.40 - -0.11)†	-0.255 (-0.40 - -0.11)†	-0.264 (-0.41 - -0.12)‡	-0.255 (-0.40 - -0.11)†	-0.223 (-0.37 - -0.08)†	-0.216 (-0.36 - -0.07)†	-0.255 (-0.40 - -0.11)*
Hospital length of stay (days) [a]	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*	*NS*
Weight at birth (SDS)	*NS*	-	-	-	-	-	-
Weight at surgery (SDS)	-	*NS*	-	-	-	-	-
Height at birth (SDS)	-	-	0.139 (0.03 – 0.25)*	-	-	-	-
Height at surgery (SDS)	-	-	-	*NS*	-	-	-
Small for gestational age	-	-	-	-	-0.457 (-0.81 - -0.10)*	-	-
Head circumference at birth (SDS)	-	-	-	-	-	0.174 (0.08-0.27)†	-
Head circumference at surgery (SDS)	-	-	-	-	-	-	*NS*

CPB, cardiopulmonary bypass surgery; DHCA deep hypothermic circulatory arrest; β, regression coefficient; CI, confidence interval; R^2, adjusted coefficient of determination

[a] Due to non-normal distribution, the natural logarithm was used for the regression analysis.

* $p<0.05$, † $p<0.01$, ‡ $p<0.001$

- not included in the model, NS included in the model but not significant

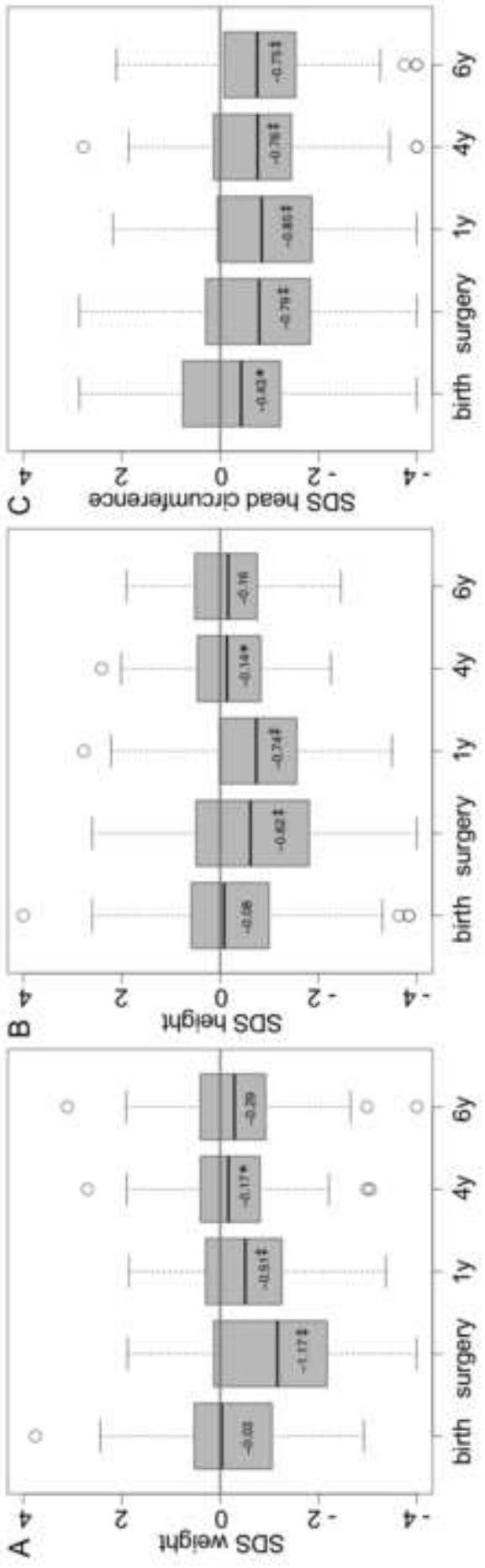

Figure 1
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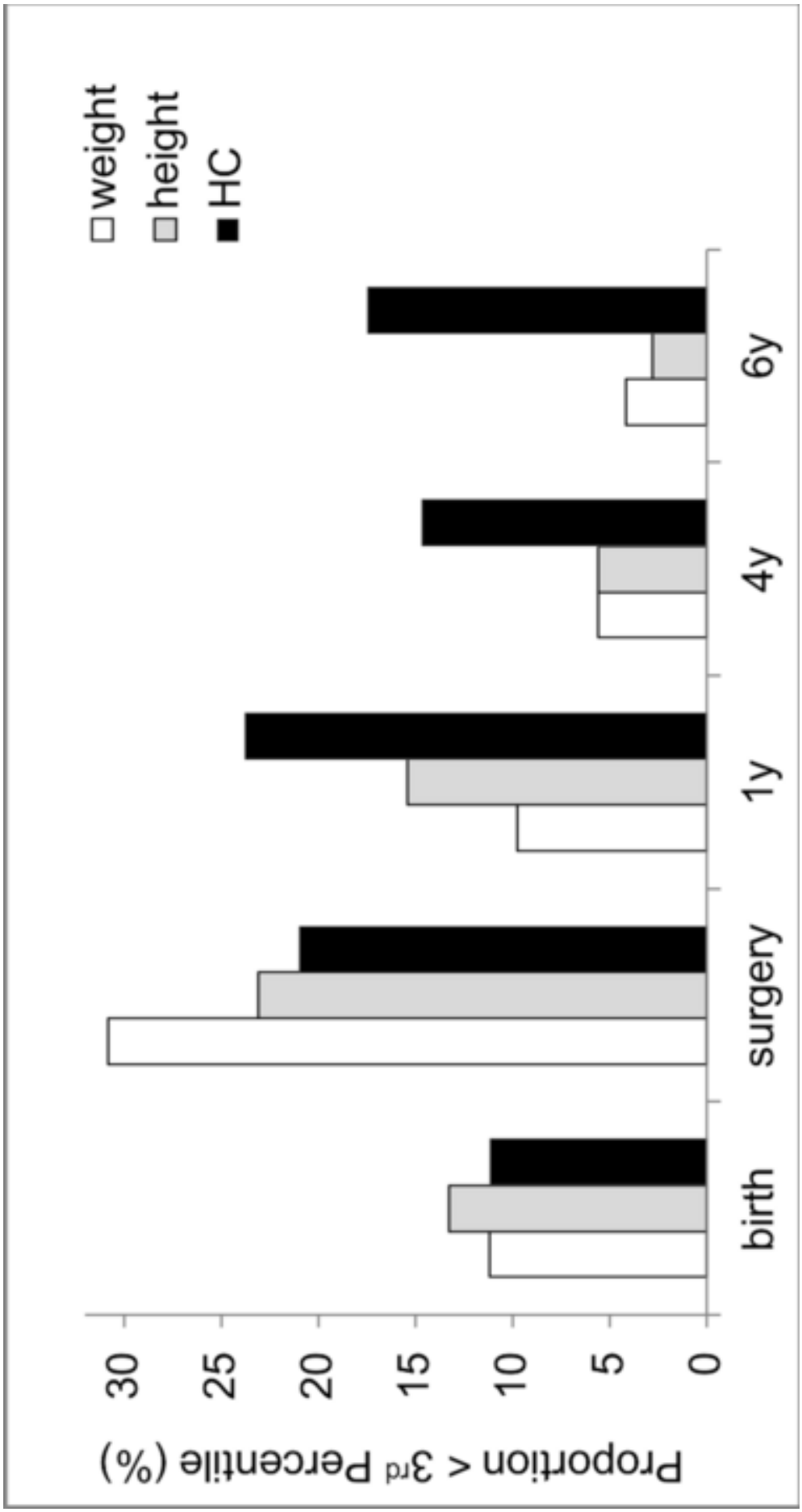

Figure 2
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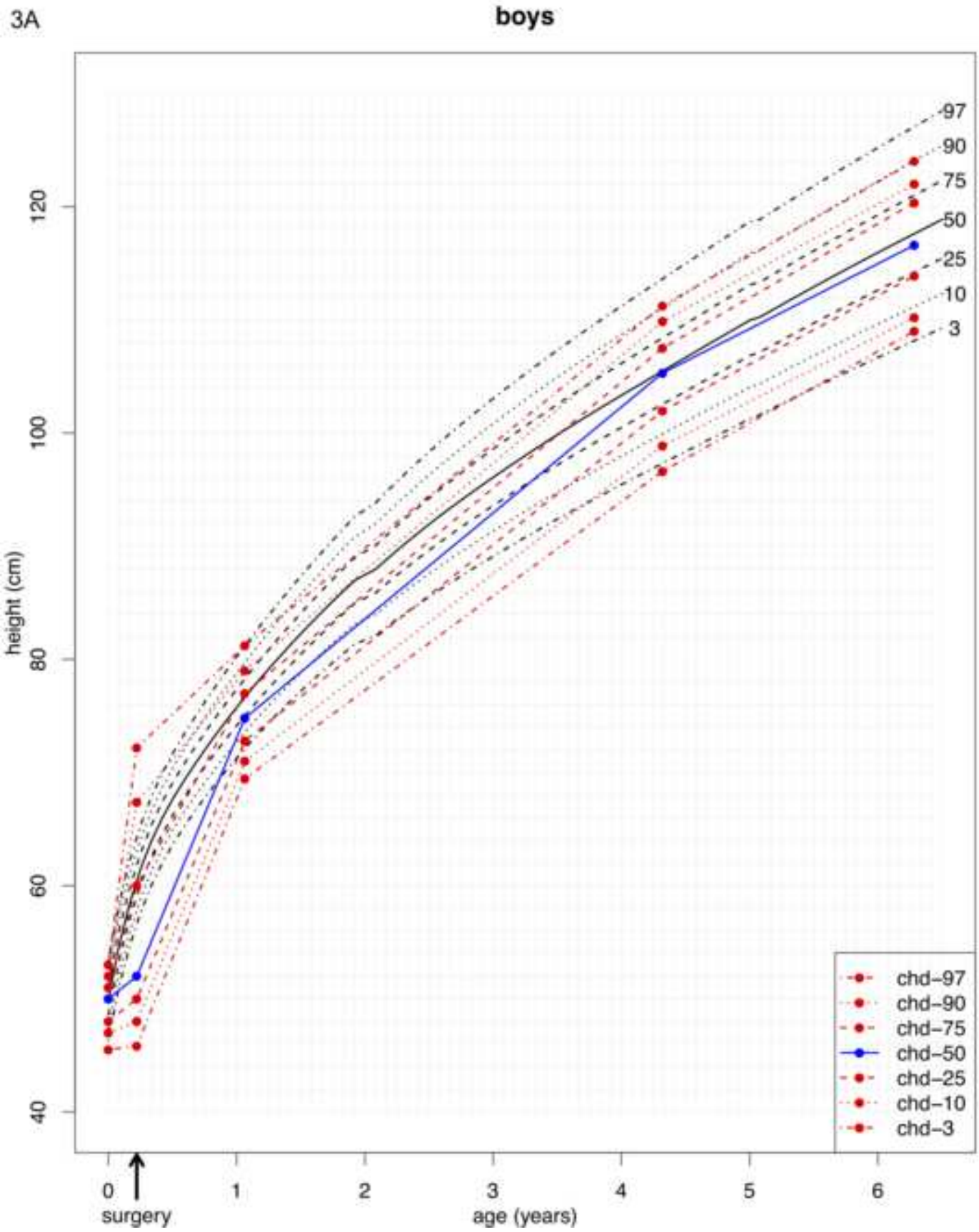

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